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Can sequences turn a profit?

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MARYLAND - Michael C. Nehls calls it "a breakthrough that is already changing how we will elucidate novel biology in order to advance medicine." He is just one among thousands of biomedical researchers who expect to profit from the public release of the draft mouse genome sequence last week.

In Nehls's case, the profit could be financial as well as intellectual. He is CEO of [Ingenium Pharmaceuticals AG](#), a Munich company that seeks to identify gene function by screening randomly mutated mice for abnormalities relevant to human disorders and then identifying which genes are involved and what they do. It took eight Ingenium researchers four years to clone the mutation that causes the so-called nude phenotype. The nude mouse is a critical model for biomedical research because it lacks a mature immune system.

Ingenium is one of the companies trying to turn genome sequences into commercial products. But commercialized genomics has undergone some notable setbacks recently. Late last month (April 2002), with considerable fanfare, [Celera Genomics](#) of Rockville, Maryland divested itself of genome sequence guru Craig Venter and announced that it would no longer try to make money by selling its human and mouse sequence data. Instead, it would exploit that data on its own behalf by turning itself into a drug development company.

Celera's decision garnered the most media attention, but it was not the only such story. Since last year, [Incyte Genomics](#), the Palo Alto, California, company formerly known as Incyte Pharmaceuticals, has been trying to return to its pharma roots. Incyte generated substantial revenue - a reported \$220 million in 2001 - selling access to some 14,000 human genes it said it had identified and applied for patents on, nearly double what Celera's data brought in. Yet Incyte, too, decided there was more money in mining its data for its own drug discovery efforts. In addition, Incyte's present executives, newly hired from the pharmaceutical industry, are shopping for potential drugs at other companies.

Incyte changed gears because of competition. Randy Scott, one of the company's founders, points out that Celera was not even on the horizon when Incyte moved from pharma into genomics in 1996-97. "It came out of nowhere and changed a lot of the dynamics of the information business. We went from having a really dominant platform to having broad competition with not only Celera but the public domain and DoubleTwist and multiple other players," Scott said. "I happen to be a big long-term believer in the power of the information market. I think we just went through a real competitive cycle where there's been a lot of weeding out of the competition. But I think that market will be robust 10 years from now, with a different competitive profile."

That competitive profile, he hopes, will include his new company, which plans to sell genomic information retail, to physicians and patients, rather than wholesale to drug companies. Scott has recently co-founded [Genomic Health Inc.](#), based in Redwood City, California, with funding from well-known venture capitalists and from Incyte itself. "We're creating a personalized genomic services company that's building genomic tests that we would provide to physicians and patients. The tests would help them make better decisions about how to treat their diseases," he says. "Our interest is in providing quality guidance to physicians so they have a good feel for which patients should get which drugs and therapies. The power of genomic information is very able to make a difference there."

The DoubleTwist model may actually have been more realistic than the proprietary approaches of Celera and Incyte, because DoubleTwist's plan was to take public data and make it useful, according to Sean Eddy, a leading bioinformaticist who is at the [Washington University School of Medicine](#), St. Louis, Missouri. Nevertheless, DoubleTwist, which was based in Oakland, California, went out of business in March. It died despite several attractive and unique products. One of them was a genome viewer, a graphics program that downloaded genome annotations onto a PC or a Mac; with the viewer, researchers could look at the genome, and do additional analysis, without being connected to the Internet.

Doug Brutlag, who was the company's chief scientist, thinks competition killed DoubleTwist too. The competition came from two places, he told *The Scientist*. First was national database resources such as GenBank at the US [National Center for Biotechnology Information](#) and [Ensembl](#) at the European Bioinformatics Institute, where tens of millions of dollars annually went into free tools for analyzing the human genome. Second, and perhaps more formidable, were large pharmaceutical firms that invested similar huge sums internally to develop their own bioinformatics groups. DoubleTwist added value to public data, but the value was not perceived as high enough for people to purchase it, says Brutlag, a bioinformaticist and professor of biochemistry and medicine at [Stanford University](#), California. "They would rather invest themselves and reinvent the wheel than purchase what DoubleTwist sold," he notes.

Does that mean making money from genome sequences is hopeless? "I think it is possible to be successful in business in this field, but there's a number of things that get in the way. Celera is a great example of a company that had very ambitious goals, invested a heckuva lot of money, but maybe didn't have a clear idea how much of a market there was for raw genomic sequence data. They had to make back \$300 million, and it's not clear the market's that big," says Eddy. He argues that there is a market for what he calls digests of interpretable data delivered regularly to the desk of an executive (or a scientist.) "The trouble is that we don't know really how to interpret the DNA sequence data very well. There isn't an accepted way of digesting it to make it interpretable to people," Eddy points out. "It's as if Lexis-Nexis started shipping digests of Tibetan runes that stayed in Tibetan runes. You'd look at it and say, 'Well, yeah, it's smaller and it's nicely indexed, but I still don't know what it means.'"

"With the public projects - in the US at the [National Institutes of Health](#) and here [in the UK] it's the [Wellcome Trust](#), a public charity - pumping in money to genome sequence, you'd have to be a bit of an idiot to base your business plan now around selling genome sequence. You've got to figure out how to add value to what these public projects are doing," counsels Ewan Birney, who leads the Ensembl genome database project at EBI near Cambridge, UK. It's not that the publicly funded genome projects are competing with private ones, he argues. "They're just raising the bar, asking everybody to concentrate on more downstream things."

Similar advice comes from Mark Swindells, who is at [Inpharmatica](#), a London company that is attempting to carve out a niche market specializing in informatics involving protein 3-D structures relevant to drug design. In a recent issue of [Genome Biology](#), he argues that fledgling companies need strong science that is visible, published in major journals, even though publication violates the usual business norms. It is not enough to have a good idea; he calls DoubleTwist's approach "a pretty neat idea," and others agree, but that did not prevent the company from going under.

DoubleTwist and the other companies may have succumbed to financial pressures similar to those that beset other industries, such as the information technology industry. Sensible players hold off on seeking

venture capital because getting it intensifies the urgency of paying off the investors, Birney points out. "This is well understood by everybody, it's just that people forget about it," he says. "If you take venture capital money you have to know how you are going to exit, because if you don't know how you're going to exit, then sure as hell the venture capitalists are going to force you to exit somehow."

That helps explain what happened to DoubleTwist, according to Eddy. "DoubleTwist did get venture capital involved very quickly, grew very quickly, became an Internet-like company, and devoted a lot of resources to complicated software development, which was maybe a little premature given the level at which we can actually interpret the data. And it ended up bleeding money." The company was unable to staunch the flow with \$75 million from a planned stock offering, which it had to cancel last year because of stock market conditions.

"I think there's a great market out there, a niche market, for people to provide good robust software and databases," Eddy says. "I'm having a hard time disconnecting the business mistakes that have been made from whether it's really possible to make money."

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